Attorney Docket No.: P-9858-US1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s):	ARBIT Ehud et al.	Examiner:	BRADLEY, Christina
Serial No.:	10/500,822	Group Art Unit:	1654
Filed:	March 14, 2005	Confirmation No.:	8526
Title:	ORAL INSULIN THERAPY		

Mail Stop AMENDMENT
Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF SHINGAI MAJURU UNDER 37 C.F.R. § 1.132

1. I was born in 1964 in Murewa, Zimbabwe.

2. In 1987, I was awarded the degree of Bachelor of Pharmacy (with Honors) from University of Zimbabwe, School of Medicine, Department of Pharmacy, in Harare, Zimbabwe. In 1990, I was awarded the degree of Master of Philosophy (Medicine) from University of Zimbabwe, School of Medicine, Department of Pharmacy, and the topic of my thesis was "Some Studies on the Megaloporous System as a Zero Order Sustained Release Matrix".

3. In 1994, I was awarded the degree of M.Sc. (Pharmaceutics) from the University of Iowa, in Iowa City, IA. In 1996, I was awarded the degree of Ph.D. Pharmaceutics from the University of Iowa, and the topic of my thesis was "The Use of Hiestand Tableting Indices to Study the Compaction Properties of Binary Powder Mixtures". Since 2005, I have been a candidate for a Masters in Business Administration, at Western Connecticut State University.

4. While a graduate student at the University of Zimbabwe from 1988-90, I was a graduate assistant and did research in the fields of: Formulation and in vivo/in vitro testing of a megaloporous system as a zero order sustained release matrix; Tablet compression and testing; UV-Vis (SP80 – 100 UV/VIS) and fluorescence polarization immunoassay; Sterile

products manufacturing (aseptic technique, horizontal laminar flow, sterilization, sterility testing); and Tablet formulation development and manufacturing.

5. While a graduate student at the University of Iowa from 1991-96, did research in the fields of: Powder compression research; Hiestand tableting indices (bonding index, brittle fracture index and strain index) as a function of composition of binary powder mixtures; Physical and mechanical characterization of pharmaceutical powder systems; Heckel analysis; and Thermal analysis (DSC, TGA and Hot Stage Microscopy).

6. From 1996-97, I was a Post Doctoral fellow at the University of Iowa, and was a laboratory manager for a preformulation/formulation project for Sepracor, Inc.; did research in solid state characterization (DSC, TGA, XRD, SEM, Particle Size Analysis, Flow Properties, Bulk, True and Tapped Density, Surface Area); supervised research assistants and postdoctoral fellows; and prepared research reports in Diffuse Reflectance Near-Infrared spectroscopy for qualitative and quantitative identification of polymorphic forms in powder materials.

7. I have been employed by Emisphere Technologies, Inc., of Tarrytown, New York since 1997 in the department of Pharmaceutics and Research and Development, as a scientist (1997-1999), a Senior Scientist (2000- 02), Associate Director (2002-03), Director (2003-05) and currently Senior Director (2006-present). In these capacities, I have been and am responsible for formulation development, pre-formulation, clinical supplies manufacture, management of new chemical entities targeted for oral delivery of macromolecules, evaluating the utility of drug delivery candidates, and leader of the team for Emisphere's lead project.

8. Thus far in my career, I have contributed to over 30 published manuscripts, abstracts and presentations, and am also a named inventor in 12 published U.S. and international patents and patent applications, as well as numerous others that have not yet been published. I believe that I am skilled in the art and subject matter of the above-identified patent application.

9. I am aware that the above-identified application was filed in the United States Patent and Trademark Office on March 14, 2005. I am familiar with this patent application and its disclosures.

10. I am also aware that the U.S. Patent and Trademark Office issued an Office Action on September 12, 2007 with regard to this patent application, wherein the Examiner rejected all of pending claims 59-91 under 35 U.S.C. § 102(e) as being anticipated by International Patent Application Publication No. WO 02/02509 (Weidner et al.), of which I am a named inventor. In that Office Action, the Examiner alleged that WO 02/02509 discloses a solid oral delivery capsule comprising zinc human recombinant insulin and the delivery agent compound 4-CNAB and a method of administering the composition to diabetic monkeys, and that the identical chemical structure taught by the prior art must inherently also have the same functional properties. However, the Examiner also admitted that he could not determine whether or not the oral solid dosage form disclosed by WO 02/02509 inherently possesses properties that anticipate the claimed invention, and the Examiner has instead shifted to the Applicants the burden of proof that this is not so.

11. I submit this declaration in support of a Response to the Office Action dated September 12, 2007. It is my opinion that the solid oral delivery capsule disclosed in the cited prior art reference WO 02/02509 would not necessarily inherently possess properties that anticipate the claimed invention, i.e., that it would not necessarily achieve a therapeutically effective reduction in blood glucose after oral administration to a human diabetic patient as compared to an untreated diabetic patient.

12. I have reviewed and am familiar with the disclosure of the cited prior art reference WO 02/02509. I am especially familiar with the teachings of WO 02/02509, as I am one of the inventors named thereon.

13. WO 02/02509 disclosed a solid oral delivery capsule comprising zinc human recombinant insulin and the delivery agent compound 4-CNAB, as taught in Example 1g on page 20 thereof. WO 02/02509 also disclosed administration of the solid oral delivery capsule to non-diabetic rats (Example 2A, at pages 21-22 thereof) and non-diabetic monkeys (Example 2B, pages 22-24 thereof). At Table 1 on page 22, WO 02/02509 provides the subject rats' mean peak serum insulin levels after administration of the solid oral delivery capsule, and at Table 1A on page 24, WO 02/02509 provides the subject monkeys' mean peak serum insulin levels and mean peak blood glucose reduction after administration of the solid oral delivery capsule.

14. WO 02/02509 provides no further analysis of the subject rats' and monkeys' blood samples. WO 02/02509 also provides no information about any administration of the solid oral delivery capsule to any other animal subjects, including diabetic animal subjects. WO 02/02509 further provides no information about any administration of the solid oral delivery capsule to humans, either diabetic or non-diabetic.

15. It is my understanding and belief that the field of biotechnology is highly unpredictable in nature and that conclusions as to the results of administration of a particular compound upon certain animals may not generally be drawn from the results of administration of that particular compound upon other animals. More importantly, conclusions as to the results of administration of a particular compound upon humans may not generally be drawn from the results of administration of that particular compound upon animals, as the results of animal studies are generally not sufficiently predictive of the results of human studies. Performing pharmacodynamic and pharmacokinetic studies concerning the administration of particular compounds to animals or humans, such as the studies described in WO 02/02509, is a painstaking process of experimentation and analysis that requires a great deal of focused time, effort and concentration and involves a great many detailed steps and analysis, both during the stages of administration and of analysis. One such study may take months or even years to complete.

16. It is my understanding and belief that it is not true that a particular compound would necessarily inherently have the same functional properties when administered to humans as it would when administered to animals. I believe that there is no reasonable expectation that results obtained when a particular compound is administered to animal subjects would also be obtained when that compound is administered to human subjects. This predictive effort is made even more difficult if the human subjects are diabetic and the animal subjects were not diabetic. In fact, I believe that it would generally require undue experimentation for one of skill in the art to determine how a particular composition would perform when administered to diabetic human subjects in comparison to untreated human subjects based upon knowledge of how that particular composition would perform when administered to non-diabetic animal subjects.

17. It is my opinion, based upon my knowledge and skill in the relevant field, that, based upon the disclosures as published in WO 02/02509, no conclusion may be drawn with regard to whether the solid oral delivery capsule disclosed in WO 02/02509 is inherently capable of yielding a therapeutically effective reduction in blood glucose after oral administration to diabetic human patients in comparison to untreated diabetic human subjects, as claimed in claims 59-91 as amended.

I declare under penalty of perjury that all statements made herein are based upon my own knowledge and believed to be true. I understand that willful false statements and the like are punishable by fine or imprisonment, or both (18 U.S.C. § 1001), and may jeopardize the validity of any patent that may be issued from the above-identified patent application.

Shingai Majuru, Ph.D. Date: February 2/7, 2008